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Intracranial hemorrhage in setting of glioblastoma with venous thromboembolism

Michael Nabil Khoury†, Symeon Missios†, Natasha Edwin, Susmita Sakruti, Gene Barnett, Glen Stevens, David M. Peereboom, Alok A. Khorana, and Manmeet S. Ahluwalia

Department of Neurooncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, Florida (M.N.K.); Department of Oncological Sciences, University of South Florida, Tampa, Florida (M.N.K.); Department of Neurosurgery, Louisiana State University, 1501 Kings Hwy, Shreveport, Louisiana (S.M.); Department of Internal Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio (N.E.); Department of Hematology/Oncology, University Hospital, 11100 Euclid Avenue, Cleveland, Ohio (S.S.); Department of Neurosurgery, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio (G.B.); Department of Neurology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio (G.S.); Department of Hematology and Oncology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio (D.M.P., A.A.K., M.S.A.); Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio (G.B., G.S., D.M.P., M.S.A.)

Corresponding Author: Michael Khoury, MD, H. Lee Moffitt Cancer Center, Department of Neurooncology, 12902 Magnolia Drive, Tampa, FL 33612-9416 (michael.khoury@moffitt.org).

†Co-first authorship: Michael N. Khoury and Symeon Missios.

Background. Venous thromboembolism (VTE) is a complication of glioblastoma. Anticoagulating patients with glioblastoma carries a theoretical risk of intracranial hemorrhage (ICH).

Methods. We performed a retrospective cohort study of consecutive glioblastoma patients (2007–2013) diagnosed with VTE.

Results. The study population comprised of 523 glioblastoma patients of whom 173 (33%) had VTE events. Seventeen (10%) had ICH: 6 (35%) subdural hematomas and 11 (65%) intratumoral hemorrhages. In total, 4 patients with ICH required neurosurgical intervention. Enhancement in the area of subsequent intratumoral hemorrhage was noted in 9 of 10 with available pre-ICH scans. Multivariable regression did not show associations between ICH and tumor enhancement diameter or use of vascular-endothelial-growth-factor inhibitor. Fifteen (16%) patients receiving anticoagulation had ICH compared with 2 (2.6%) not receiving anticoagulation ($P = .005$). The method of anticoagulation was not associated with development of ICH. Median survival times from nondistal VTE diagnosis to death were 8.0 and 3.5 months ($P = .05$) in patients receiving anticoagulation and those not on anticoagulation, respectively.

Conclusion. Patients with glioblastoma and VTE on anticoagulation have increased incidence of ICH. However, development of ICH was not associated with lower median survival from time of VTE. Intratumoral hemorrhage occurred within the enhancing portion of tumor; however, no relationship was identified between the development of ICH and (i) the median diameter of enhancement or (ii) type of anticoagulant used. However, patients with absence of enhancing tumor did not have intratumoral bleed, suggesting gross total resection may limit this adverse outcome. It is appropriate to initiate anticoagulation in glioblastoma patients with VTEs.

Keywords: anticoagulation, glioblastoma, intracranial hemorrhage, search terms, venous thromboembolism.

Development of venous thromboembolism (VTE), which includes deep venous thrombosis (DVT), pulmonary embolism (PE), and, less frequently, cerebral venous sinus thrombosis, is a common complication of malignancy.[1,2] Patients with high-grade gliomas are particularly susceptible to this adverse event with reported incidences of 24% to 37%.[3–5] The risk of VTE is increased in the postoperative period but continues through the course of the disease.[6,7] The highly vascular nature of glioblastoma and risk of intracranial hemorrhage (ICH) may delay appropriate anticoagulation following diagnosis of a VTE. Prior studies of ICH in the setting of

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anticoagulation for VTE in high-grade gliomas demonstrate an incidence of ~2%, similar to the incidence of ICH in the absence of anticoagulation.[4,8]

Using a cohort comprised exclusively of patients diagnosed with glioblastoma (WHO grade IV) and concomitant VTE, we retrospectively investigated the incidence of ICH in setting of VTE with and without anticoagulation. We further sought to identify risk factors for ICH, including the type of anticoagulation. Finally, we reviewed the neuroimaging characteristics of ICH in patients with glioblastoma.

Methods

Data compilation

In this IRB approved study, the records of 523 consecutive patients with histologic diagnosis of glioblastoma from 2007 to 2013 were reviewed. Diagnoses of DVT (proximal or distal), PE, and cerebral venous sinus thrombosis constituted VTE events. Proximal DVT was defined as thrombus occurring in the popliteal vein or above. The diagnosis was made on the basis of Doppler ultrasound, chest computed tomography, or magnetic resonance venography as documented in the electronic records. The demographics and medical history of patients with a documented VTE were recorded. The clinical history, including extent of surgical resection, radiation therapy, chemotherapy, and use of vascular endothelial growth factor (VEGF) inhibitor, was also documented. The method of anticoagulation—if any—was also recorded. Patients with spinal glioblastoma and patients younger than 18 years were excluded. Patients with ICH prior to the VTE diagnosis were also excluded from the analysis.

Image review

Evidence of ICH following the diagnosis of VTE was determined based on medical record and neuroimaging review. The location of the ICH (subdural/intratumoral/intraventricular) was determined based on a review of the available neuroimages (CT or MRI). Patients with evidence of hemorrhage in the immediate postoperative period (<7 days) or with intratumoral petechial hemorrhage noted on susceptibility-weighted imaging (SWI) MRI sequences were not included in the ICH subgroup. Enhancing tumor measurements were obtained in the longest diameter axis on either axial or coronal planes from neuroimaging completed no longer than 40 days from VTE diagnosis.

Statistical analysis

Patient characteristics were summarized using frequency counts for categorical variables and using medians, means and ranges for continuous variables. Continuous variables were presented with the mean and standard deviation or the median and interquartile range (IQR) as appropriate, whereas categorical values were presented as percentages. Continuous variables were compared using a Student's *t*-test or Mann-Whitney test, as appropriate, and categorical variables were compared using the chi-square test. Survival data were summarized using Kaplan-Meier methods and comparisons were made using the log-rank test (Mantel-Cox). Univariate and multivariable analyses were employed to evaluate the potential prognostic factors for development of ICH using the SPSS v20.0 package (IBM Corp.).

Results

Patient characteristics

VTE location and treatment characteristics

One hundred seventy-three (33.1%) of the 523 patients with glioblastoma developed at least 1 VTE event during the follow-up period. One-hundred thirty-eight (79.8%) developed DVT, 20 (11.6%) both DVT and PE, 14 (8.1%) PE, and 1 (0.6%) patient developed sagittal sinus thrombosis. Within the DVT subgroup, 74 patients had exclusively distal DVTs without involvement of other sites; 32 (43.2%) of these patients received anticoagulation. Ninety-nine patients had a VTE involving a site other than a distal VTE; of these, 65 (65.7%) received anticoagulation, 29 underwent inferior vena cava (IVC) filter placement alone, 1 patient underwent thrombectomy, and 4 did not receive any intervention due to complications including thrombocytopenia or bleeding. In total, 77 patients received an IVC filter; 43 (55.8%) as the solitary intervention and 34 (44.2%) with concurrent anticoagulation. Finally, of the 97 patients receiving anticoagulation, 69 (71.1%) were treated with low molecular weight heparin (LMWH), 26 (26.8%) with warfarin, and 2 (2.1%) with heparin as inpatients (1 IV heparin and 1 subcutaneous heparin).

Demographics, tumor diameter

The median age of patients was 65 years (range 34–89 years), and 117 (67.6%) were under age 70. Ninety-three patients (53.8%) had a KPS $\geq$ 70. The group consisted of 66 females (38.2%) and 107 males (61.8%). Mean body mass index (BMI) was 29.5. Comorbidities and demographics are demonstrated in Table 1. Mean diameter of the enhancing portion of the tumor at time of VTE was 37.0 mm. The median length of follow-up was 6.1 months.

Surgical, radiation, and chemotherapy treatment

A gross total resection was completed in 48 (27.7%) patients, a subtotal resection in 47 (27.2%), and a near total resection in 27 (15.6%). Forty-eight (27.7%) patients underwent stereotactic biopsy alone and 3 (1.7%) underwent laser interstitial thermal therapy (LITT). Thirty-nine patients (22.5%) were undergoing radiation therapy, while 70 patients (40.4%) were on chemotherapy (not including those receiving only bevacizumab) at time of VTE diagnosis. Twenty-one patients (12.1%) were on a VEGF inhibitor (20 bevacizumab and 1 ramucirumab) at the time of VTE diagnosis.

VTE diagnosis is common in the preoperative evaluation and in the perioperative period

The median length of time from pathologic diagnosis of glioblastoma to VTE diagnosis was 1.4 months. However, 19 patients (10.9%) were diagnosed with a VTE during the preoperative evaluation. In total, 51 patients (29.5%) developed a VTE during the perioperative period (within 7 days of surgery).

ICH vs non-ICH comparisons

Higher KPS but not age is associated with ICH

Seventeen patients (9.8%) developed an ICH following the diagnosis of VTE, while 153 (90.2%) did not. The median age (range

Table 1. Demographics of patients with glioblastoma and venous thromboembolism organized according to intracranial hemorrhage (ICH) status

	All Patients		Non-ICH		ICH		*P* value
Sample size	173		156		17		
		IQR		IQR		IQR	
Median age	65	16	65	18	64	16	.5
		SD		SD		SD	
BMI	29.5	5.3	29.4	5.4	30.2	4.7	.5
Initial tumor diameter (mm)	42.7	16.3	42.7	16.8	40.1	13.7	.5
Enhancement diameter (mm)	37.0	17.8	36.4	18.0	42.2	15.2	.8
		%		%		%	
Sex							
Female	66	38.2	59	37.8	7	41.2	.8
Male	107	61.8	97	62.2	10	58.8	
Age >70	56	32.4	50	32.1	6	35.3	.8
KPS ≥ 70	93	53.8	79	50.6	14	82.4	.013
Comorbidities							
CKD	4	2.3	4	2.6	0	0	.5
COPD	10	5.8	8	5.1	2	11.8	.3
Heart Failure	3	1.7	3	1.9	0	0	.6
DM	34	19.7	33	21.2	1	5.9	.13
CAD	13	7.5	13	8.3	0	0	.2
Hyperlipidemia	72	41.6	67	42.9	5	29.4	.3
Hypertension	99	57.2	94	60.3	5	29.4	.02
Smoking	5	2.9	5	3.2	0	0	.5
Alcohol	2	1.2	2	1.3	0	0	.6
Other malignancy[a]	25	14.5	23	14.7	2	11.8	.7
Surgery							
Biopsy	48	27.7	42	26.9	6	35.3	.5
STR	47	27.2	44	28.2	3	17.6	.3
NTR	27	15.6	25	16	2	11.8	.6
GTR	48	27.7	43	27.6	5	29.4	.9
LITT	3	1.7	2	1.3	1	5.9	.2

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; STR, subtotal resection; NTR, near total resection; GTR, gross total resection; LITT, laser-induced thermal therapy; IQR, interquartile range; SD, standard deviation.
[a]Three patients had more than one malignancy. The various malignancies included: prostate cancer (9), basal cell carcinoma (4), breast cancer (3), meningioma, ovarian cancer, colorectal cancer, thyroid cancer, laryngeal cancer, T-cell non-Hodgkin's lymphoma, renal cell carcinoma, small cell lung cancer, salivary gland cancer, melanoma, squamous cell skin cancer, other skin cancer (not specified).

42–81 years) of ICH patients was 64 compared with 65 years in the non-ICH group ($P = .5$). The percentage of patients with an age >70 years was also similar between the two groups; 6 patients (35.3%) and 50 patients (32.1%), respectively ($P = .8$). Meanwhile, the incidence of a KPS ≥ 70 was greater in the ICH group than the non-ICH group; 14 of 17 patients (82.4%) vs 79 of 156 patients (50.6%), respectively ($P = .013$).

Degree of surgical resection was not associated with incidence of ICH

Five of 48 patients (10.4%) who underwent gross total resection during initial surgical intervention developed ICH ($P = .9$). Two of 27 patients (7.4%) with near total resection developed ICH ($P = .6$), and 3 of 47 patients (6.4%) with subtotal resection would later develop ICH ($P = .3$). Meanwhile, of 48 patients undergoing biopsy only, 6 patients (12.5%) developed ICH ($P = .5$). Three patients underwent a LITT procedure, and 1 later developed ICH ($P = .2$).

Patients receiving anticoagulation have an increased incidence of developing ICH

Fifteen of the 97 patients (15.5%) receiving anticoagulation developed an ICH, while 2 of the 76 patients (2.6%) not receiving anticoagulation developed an ICH ($P = .005$) (Table 2). Univariate analysis suggested that anticoagulation is predictive of developing ICH (OR = 6.7; 95% CI, 1.5–30.3; $P = .013$)

Table 2. Venous thromboembolism (VTE) location and anticoagulation status according to intracranial hemorrhage (ICH) status

Anticoagulation status	All Patients		Non-ICH		ICH		P value
None	76	43.9	74	47.4	2	11.8	
Anticoagulated	97	56.1	82	52.6	15	88.2	.005
Method of anticoagulation							
Warfarin	26	26.8	23	28.0	3	20.0	.5
Heparin	2	2.1	1	1.2	1	6.7	.17
Low molecular weight heparin	69	71.1	58	70.8	11	73.3	.8
IVC filter	77	44.5	66	42.3	11	64.7	.08
Radiation at time of VTE	39	22.5	35	23.2	4	25.0	.9
Chemotherapy at time of VTE	70	40.4	60	39.5	10	58.8	.10
VEGF-inhibitor use at time of VTE	21	12.1	19	12.2	2	11.8	.9
VTE Location							
DVT	138	79.8	127	81.4	11	64.7	.10
Proximal LE	55	31.8	48	30.8	7	41.2	.4
Distal LE	74	42.8	71	45.5	3	17.6	.03
UE	6	3.5	5	3.2	1	5.9	.6
UE + LE	3	1.7	3	1.9	0	0	.6
PE	14	8.1	9	5.8	5	29.4	.001
DVT and PE	20	11.6	19	12.2	1	5.9	.4
Other[a]	1	0.6	1	0.6	0	0	.7

Abbreviations: IVC, inferior vena cava; VEGF, vascular endothelial growth factor; DVT, deep venous thrombosis; PE, pulmonary embolism; LE, lower extremity; UE, upper extremity.
[a]Sagittal sinus thrombosis.

(Table 3); however, on multivariable analysis, the trend remained but was less robust (OR = 9.3; 95% CI, 0.92–90.9; $P = .06$).

There is no association between the type of anticoagulation used and development of ICH

Of the 26 patients receiving warfarin, 3 patients (11.5%) developed an ICH ($P = .5$). Eleven patients receiving low-molecular weight heparin, (11/69, 16.4%) developed an ICH ($P = .7$). Two patients received heparin and one of the patients developed an ICH ($P = .17$). On univariate analysis no association was identified between type of anticoagulation and risk of developing ICH ($P = .6$). The international normalized ratios (INR) of the three individuals receiving warfarin at time of ICH were 2.5, 3.1, and 2.0.

Vascular endothelial growth factor (VEGF) inhibitor use did not predict ICH

Of 21 patients treated with a VEGF inhibitor during VTE diagnosis, 2 patients were on a VEGF inhibitor at the time of ICH ($P = .9$). On univariate analysis, VEGF inhibitor use was not predictive of ICH ($P = .9$). Of 24 patients treated with concurrent anticoagulation and VEGF inhibitors, 2 patients (8.3%) developed ICH; meanwhile, of 73 patients treated with anticoagulation in the absence of VEGF inhibitor use, 13 patients (17.8%) developed ICH ($P = .3$).

Table 3. Univariate analysis of various factors and incidence of intracranial hemorrhage

Variable	OR	95% CI	P value
Anticoagulation	**6.7**	**1.5–30.3**	**.013**
Age	0.98	0.94–1.03	.5
Gender	1.15	0.42–3.19	.8
BMI	1.03	0.94–1.13	.5
COPD	2.47	0.48–12.7	.3
DM	0.23	0.03–1.82	.17
Hyperlipidemia	0.55	0.19–1.65	.3
Hypertension	**0.27**	**0.09–0.82**	**.02**
Cancer history	0.77	0.17–3.60	.7
EGFR status	0.72	0.24–2.20	.6
Diameter of enhancing tumor at time of VTE	1.02	0.99–1.05	.2
Diameter of initial tumor	0.99	0.96–1.02	.5
Extent of resection	0.97	0.64–1.46	.9
VEGF-inhibitor at time of VTE	0.98	0.21–4.63	.9
VEGF-inhibitor use during any period	0.83	0.26–2.68	.8
Distal LE DVT	**0.25**	**0.07–0.90**	**.035**
Anticoagulation for pulmonary embolus	2.2	0.69–6.9	.2
Method of anticoagulation	1.1	0.6–2.3	.6

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EGFR, epidermal growth factor receptor; VTE, venous thromboembolism; VEGF, vascular endothelial growth factor; LE DVT, lower extremity deep venous thrombosis.

Patients with hypertension did not have an increased incidence of ICH

Hypertension was present in 5 (29.4%) of 17 patients with ICH and 94 (60.3%) of 156 patients without ICH ($P = .02$). In patients with ICH, the median and mean systolic blood pressures at time of ICH diagnosis were 137 mm Hg and 132 mm Hg, respectively (range: 105–175 mm Hg).

Median survival time from VTE diagnosis to death was similar in ICH and non-ICH groups

The median survival time from VTE diagnosis to death in the ICH group was 7.2 months, compared with 6.2 months in the non-ICH group ($P = .4$).

The majority of patients with ICH did not require neurosurgical interventions

Four of the 17 patients with ICH had a subclinical presentation of hemorrhage and detected only by routine imaging. Eleven patients required hospitalization. Four patients with ICH required neurosurgical intervention. In all, 2 (1 on anticoagulation) of the 17 patients died within a month of ICH diagnosis as inpatients from complications directly related to the hemorrhage, and 2 patients (both on anticoagulation) died as outpatients within a month of ICH diagnosis after their care was transitioned to hospice. Table 4 documents the severity of the ICH in our cohort.

Table 4. Radiologic and clinical characteristics of patients who developed intracranial hemorrhage (ICH)

Pt #	ICH location	Hemorrhage within enhancing tumor	Enhancing area diameter (mm) at time of VTE diagnosis	Anticoagulation	Overall survival from VTE diagnosis (months)	Neurosurgical intervention for ICH	Hospitalization required for ICH	ICH presentation	Catastrophic hemorrhage[b]	Comment	VEGFi at time of ICH
1	subdural	n/a	41	warfarin	39.8[a]	−	yes	clinical	−		−
2	subdural	n/a	73	warfarin	9.1	−	yes	clinical	−		−
3	subdural	n/a	38	LMWH	39.9[a]	−	no	subclinical	−		−
4	subdural	n/a	28	LMWH	5.5	−	yes	clinical	−		−
5	subdural	n/a	images not available	LMWH	7.2	−	no	subclinical	−		−
6	subdural	n/a	28	none	1.0	+	no	clinical	+		−
7	intratumoral	+	29	LMWH	5.3	−	yes	clinical	+	made hospice, discharged	−
8	intratumoral	+	56	warfarin	12.7	−	yes	clinical	−		+
9	intratumoral with intraventricular extension	−	42	LMWH	3.0	−	no	subclinical	+	made hospice, discharged	−
10	intratumoral	+	55	LMWH	14.5	−	yes	clinical	−		−
11	intratumoral with intraventricular extension	+	17	LMWH	5.0	−	yes	clinical	+	DNR/I	+
12	intratumoral	+	56	LMWH	11.5	−	yes	clinical	−		−
13	intratumoral	+	55	LMWH	18.4	+	yes	clinical	−		−
14	Intratumoral	+	32	LMWH	5.8	−	yes	clinical	−		−
15	intratumoral with intraventricular extension	images not available	images not available	LMWH	7.8	+	yes	clinical	−		−
16	intratumoral	+	53	heparin infusion	2.7	+	no	clinical	−		−
17	Intratumoral	+	30	none	6.2	−	no	subclinical	−		−

n/a, not applicable.
Abbreviations: LMWH, low molecular weight heparin; VEGFi, vascular endothelial growth factor inhibitor; VTE, venous thromboembolism.
[a]Alive.
[b]Passed away within 1 month directly from bleeding complication (either during admission or decision made to withdraw care to home hospice following ICH).

Significant thrombocytopenia was not a major factor in developing ICH

Of the 17 patients with ICH, only 2 had platelet counts $<75 \times 10^3$/microL (54×10^3/microL and 57×10^3/microL), while 3 patients had platelet counts $<100 \times 10^3$ microL (92×10^3/microL). The median and mean platelet counts of patients with ICH were 148×10^3/microL and 160×10^3/microL, respectively (range: 54-282 $\times 10^3$/microL).

VTE intervention outcomes

Patients receiving anticoagulation tended to be younger but without a significant difference in KPS score than those not receiving anticoagulation

The median age of patients receiving anticoagulation as therapy for VTE was 63 years (range 34–73 years) compared with 68 years (range 43–89 years) in those not treated with anticoagulation ($P = .003$). However, 57 (58.8%) out of 97 patients receiving anticoagulation had a KPS score ≥70. In comparison, 36 (47.4%) out of 76 patients not receiving anticoagulation had a KPS score ≥70 ($P = .14$) (Table 5).

Patients with VTE diagnosis during the preoperative evaluation or the perioperative period have a greater incidence of not receiving anticoagulation than patients with VTE diagnosis at a later stage

Of the 19 patients with VTE diagnosis during the preoperative evaluation, 7 patients (36.8%) received anticoagulation and 12 (63.2%) did not ($P = .073$). Meanwhile, of the 51 patients with perioperative VTE diagnosis, 13 patients (25.5%) were therapeutically anticoagulated while 38 (74.5%) did not receive anticoagulation ($P < .0001$).

Patients with VTE diagnosis during chemotherapy or VEGF-inhibitor treatment were therapeutically anticoagulated more often than those off treatment

Of 70 patients with VTE diagnosis during chemotherapy, 52 patients (74.3%) were therapeutically anticoagulated. Meanwhile, 18 of the 70 patients (25.7%) receiving chemotherapy were not anticoagulated ($P < .0001$). Of 21 patients on a VEGF inhibitor at the time of VTE diagnosis, 19 patients (90.5%) were therapeutically anticoagulated, while 2 of 21 patients (9.5%) on a VEGF inhibitor were not anticoagulated ($P = .001$).

Table 5. Characteristics of patients with glioblastoma and venous thromboembolism (VTE) organized according to anticoagulation status

	All Patients		Nonanticoagulated		Anticoagulated		*P* value
Sample size	173		76		97		
		IQR		IQR		IQR	
Median age	65	16	68	18	63	15	.003
		SD		SD		SD	
Initial tumor diameter (mm)	42.7	16.3	44.1	16.9	41.1	16.2	.3
Enhancement diameter (mm)	37.0	17.8	37.3	16.2	36.8	19.0	.9
		%		%		%	
Age >70	56	32.4	33	43.4	23	23.7	.006
KPS ≥ 70	93	53.8	36	47.4	57	58.8	.14
Sex							
Female	66	38.2	34	44.7	32	33.0	.11
Male	107	61.8	42	55.3	65	67.0	
ICH status							
+	17	9.8	2	2.6	15	15.5	.005
−	156	90.2	74	97.4	82	84.5	
Radiation at time of VTE	39	22.5	13	18.3	26	26.8	.13
Chemotherapy at time of VTE	70	40.5	18	25.0	52	53.6	<.0001
VEGF-inhibitor use at time of VTE	21	12.1	2	2.7	19	19.6	.001
IVC filter	77	44.5	43	56.6	34	35.1	.005
		95% CI		95% CI		95% CI	
Median time (months) from VTE to death	6.4	5.1–7.8	4.7	2.6–6.9	7.9	6.7–9.3	.07
Median time (months) from nondistal VTE to death	6.9	5.0–8.8	3.5	1.5–5.4	8.0	6.5–9.5	.05
Median time (months) from distal VTE to death	6.0	4.3–7.8	5.8	3.1–8.4	7.2	3.7–10.7	.24
Median time (months) from glioblastoma diagnosis to death	10.2	8.5–11.9	6.1	3.5–8.8	13.4	10.9–15.8	<.001

Abbreviations: KPS, Karnofsky Performance Status; ICH, intracranial hemorrhage; VEGF, vascular endothelial growth factor; IVC, inferior vena cava; IQR, interquartile range; SD, standard deviation.

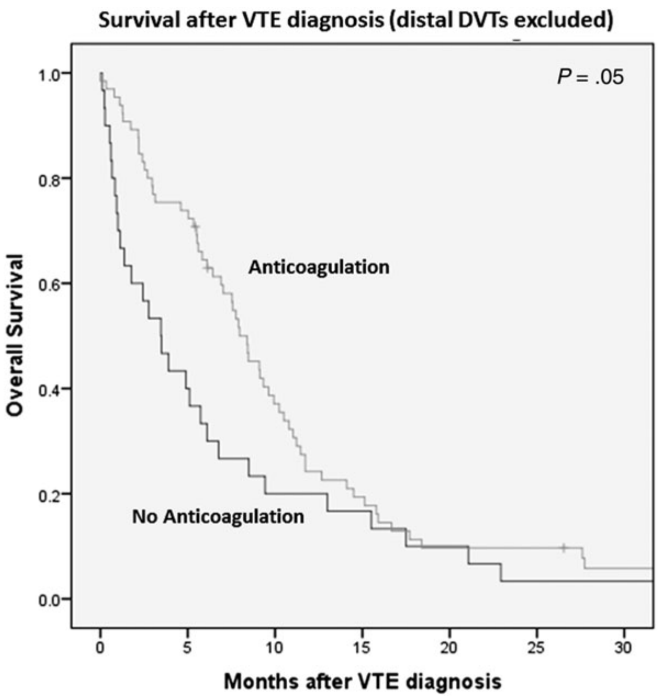

Fig. 1. Survival after VTE diagnosis. The median post-VTE survival for patients receiving anticoagulation (lightly shaded line) was 8.0 months compared with 3.5 months for those not receiving anticoagulation (darkly shaded line). Patients with only distal DVTs were excluded. Abbreviations: VTE, venous thromboembolism; DVT, deep venous thrombosis.

Survival following VTE diagnosis was longer for patients treated with anticoagulation than for those not therapeutically anticoagulated

The median survival post-VTE diagnosis was 7.9 months for patients treated with anticoagulation and 4.7 months for those not therapeutically anticoagulated ($P = .07$) (Supplementary Fig. S1). When distal DVTs were excluded from the analysis, the median post-VTE diagnosis length of survival was 8.0 months in the anticoagulated group and 3.5 months in patients not receiving anticoagulation ($P = .05$) (Fig. 1). In patients with distal DVTs only, the median post-VTE diagnosis length of survival is 7.2 months and 5.8 months in the therapeutically anticoagulated and non-anticoagulated groups, respectively ($P = .24$).

Method of anticoagulation was not associated with difference in survival post-VTE diagnosis

Median survival for patients receiving heparin was not reached. Patients who received warfarin had a median survival of 9.9 months post-VTE diagnosis (CI, 6.1–13.7), compared with a median survival of 6.9 months (CI 4.8–9.0) for those treated with low-molecular weight heparin ($P = .9$).

In patients not receiving anticoagulation, IVC filter placement was not associated with increased survival

Of the 76 patients not receiving anticoagulation, 43 (56.6%) were managed with IVC filter placement. The median survival following VTE diagnosis was 4.7 months for patients managed with IVC filters and 4.9 months for those managed without IVC filters. ($P = .97$). The percentage of patients with IVC filters who had a KPS ≥ 70 was 58.1% (25/43), compared with 33.3% (11/33) of those without IVC filters ($P = .03$).

Neuroimaging characteristics of ICH

Intracranial hemorrhage location

In total, 17 patients developed intracranial hemorrhage, of which 6 (35.3%) were subdural hematomas and 11 (64.7%) were intratumoral hemorrhages. The 11 intratumoral hemorrhages were comprised of 8 purely intratumoral hemorrhages and 3 intratumoral hemorrhages with intraventricular extension.

Intratumoral hemorrhage typically occurs within the enhancing portion of tumor

Of the 11 patients with intratumoral hemorrhages, 10 had neuroimaging available within 40 days prior to the ICH date. Enhancement in the area of subsequent intratumoral hemorrhage was noted in 9 of the 10 scans (Fig. 2); while enhancing tumor was appreciated directly adjacent to the location of the intratumoral hemorrhage in the single exception.

Enhancing tumor diameter is not predictive of ICH development

Mean diameter of enhancing tumor portion at time of VTE diagnosis was 42.2 mm in the ICH group compared with 36.4 mm in the non-ICH group ($P = .8$) Further, on univariate analysis, the diameter of enhancing tumor was not predictive of ICH ($P = .2$).

Patients without enhancing tumors did not develop intratumoral hemorrhages

Six patients had nonenhancing tumor on neuroimaging at time of VTE diagnosis, 5 of whom received anticoagulation. None of these patients developed an intratumoral hemorrhage (or subdural hematoma). The smallest size of enhancing tumor at time of VTE diagnosis with subsequent ICH was 17 mm. In total, 16 patients had enhancing tumor diameter <17 mm at time of VTE diagnosis.

Overall survival

The median overall survival from time of glioblastoma diagnosis of all VTE patients was 10.2 months. The median overall survival of patients who received anticoagulation vs those not treated was 13.4 vs 6.1 months, respectively ($P < 0.001$). The median overall survival of patients who developed ICH and those who did not was 12.2 vs 10.0 months, respectively ($P = .4$). Within the ICH group, the median overall survival for those with subdural hematomas compared with those with intratumoral hemorrhages was 9.9 and 13.4 months, respectively ($P = .5$).

Discussion

This study provides insight regarding intracranial hemorrhages in glioblastoma patients receiving anticoagulation for VTE. First, we demonstrate that the incidence of ICH in this population is

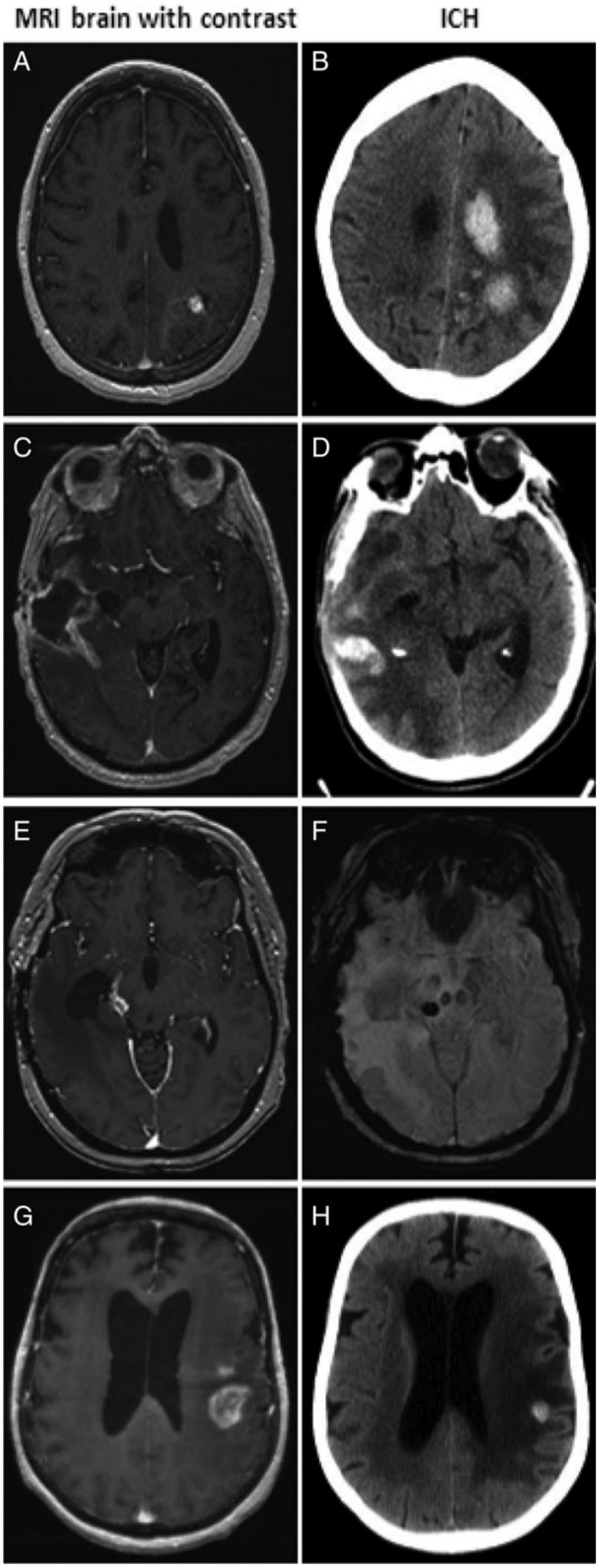

Fig. 2. Hemorrhage within enhancing tumor component. (A) T1-weighted MRI with contrast of a patient treated with enoxaparin with a noncontrast CT head, (B) obtained 4 weeks later demonstrating hemorrhage within the enhancing tumor with intraventricular extension; (C) T1-weighted MRI with contrast of a patient on enoxaparin with a noncontrast CT head, (D) obtained ~4 weeks later demonstrating hemorrhage within the enhancing tumo; (E) T1-weighted MRI with contrast of a patient on enoxaparin with MRI SWI, (F) obtained 4 weeks later demonstrating a hemorrhage within enhancing tumor extending into the rostral midbrain; (G) T1-weight MRI with contrast of a patient treated with warfarin with a non-contrast CT head, and (H) obtained 11 days later demonstrating hemorrhage within the enhancing tumor component. Abbreviation: SWI, susceptibility-weighted imaging.

greater than previously reported. Ruff and Posner reported an ICH incidence of 1.9% in a series of 103 patients with malignant gliomas receiving anticoagulation.[4] However, the distribution of tumor grades was unclear, as the term 'malignant glioma' was not clearly defined. Our study exclusively involved patients with WHO grade IV gliomas. The study also did not define the location of the intracranial hemorrhage by not specifying intraaxial or extraaxial location, and was also published in 1983 and thus relied on CT scans to determine absence or presence of hemorrhage. While CT images are sensitive in acute hemorrhage, MRI with SWI and gradient echo (GRE) sequences were used in the majority of our patients and are more sensitive in the detection of clinically silent microbleeds and subdural hematomas in the subacute phase.[9] A more recent study in 2009 investigated the incidence of VTE and ICH in glioblastoma patients. Of 25 patients receiving anticoagulation, 3 patients (12%) developed ICH; although only one case was considered by the authors to be directly related to anticoagulation.[8] Although the sample size of that study might be too small to draw firm conclusions, the results are similar to the 15.5% ICH incidence rate in anticoagulated glioblastoma patients in our study.

Our results indicate that patients who were anticoagulated tended to have longer post-VTE diagnosis survival and overall survival than patients with VTE who did not receive therapeutic anticoagulation. Although the age difference between the two groups did reach statistical significance, the difference is quite small and of uncertain clinical significance. Additionally, the difference in percentage of patients with KPS scores ≥70 in the two groups was not statistically significant. The lower post-VTE diagnosis and overall survival in patients treated with IVC filters is also consistent with well-established data, suggesting that their use should be limited to patients with otherwise clear contraindications to anticoagulation and as temporary measure.[10,11] The survival data of our cohort further support consideration for treatment with anticoagulation in patients with glioblastoma with VTE 0.[12] This difference in survival was particularly evident in those with proximal DVTs—a population that has a markedly increased risk of developing pulmonary embolism. On the other hand, there are no clear practice guidelines on when to anticoagulate patients with distal DVTs. The post-VTE survival data that we present neither support nor discourage anticoagulation in the distal DVT patient population. Several clinical factors that may have played a role in the clinical decision to anticoagulate may have had an indirect effect on patient survival and are not easily accounted for in a retrospective study. These include a clinically appropriate selection bias on who may tolerate anticoagulation based on medical comorbidities as well as where in the disease course the patient was at the time of VTE diagnosis.

Our data did not demonstrate an association between the method of anticoagulation and incidence of ICH. This finding may be important in the clinical setting as practitioners weigh multiple factors in determining the optimal type of anticoagulant including costs, method of administration, rate of VTE recurrence, and patient comfort and reliability.[13] A limitation of our study is its retrospective nature and additional prospective studies will be required to confirm our observation, with possible inclusion of the newer anticoagulants such as the oral direct factor Xa inhibitors.[14]

In 2007, Nghiemphu et al reported 21 patients who received anticoagulation and bevacizumab concurrently. Of those, 3 patients had small intracerebral hemorrhages visualized on MRI and only one developed symptoms.[15] In comparison, our study reports a slightly lower ICH incidence with concurrent anticoagulation and VEGF-inhibitor use. Moreover, our study demonstrates that patients treated with anticoagulation and VEGF inhibitors concurrently did not have a higher incidence of ICH than patients on anticoagulation alone.

The high rate of VTE diagnosed during the preoperative and perioperative periods highlights the importance of frequent monitoring and preventive measures. Patients should be evaluated for the presence of perioperative VTEs. Additionally, aggressive use of pneumatic compression devices, early patient mobilization and subcutaneous prophylactic heparin should be initiated as early as 24 to 48 hours postoperatively.[16] Meanwhile, current literature does not support initiation of therapeutic anticoagulation within 48 hours of an intracranial procedure.[17] Patients with complex postoperative courses that preclude initiation of anticoagulation prior to discharge should be re-evaluated upon outpatient follow-up for optimal initiation of appropriate anticoagulation. This underlines the importance of effective communication between the surgical and oncology teams and the benefits of a multidisciplinary approach.

Patients who developed ICH tended to have a higher KPS and 30% sustained subdural hematomas, which raises concern that part of the greater incidence of ICH in anticoagulated patients might be a result of traumatic falls from patients who were more active. The study methodology did not account for number of falls during treatment/follow-up or immediately prior to ICH. Nonetheless, it is a reminder that fall risks and gait disturbances in patients with glioblastoma should be frequently assessed with prompt referral to physical therapy for gait rehabilitation.[18] Additionally, impaired executive function is linked with poor attention to gait.[19] Hence, a subset of glioblastoma patients might benefit from dual physical and cognitive therapy to minimize fall risk.[20,21] Other factors that increase risk of falls should also be eliminated, and can be accomplished, in part, by providing appropriate seizure management and reducing the possibility of proximal muscle weakness related to steroid myopathy by promptly, yet safely, tapering steroids.[22,23]

Hypertension was not predictive of developing ICH; a finding that provides further understanding of the pathophysiology of intratumoral hemorrhage. Our review of the neuroimaging showed that intraaxial hemorrhages occurred within the tumor—overwhelmingly within the enhancing portion—rather than areas classically susceptible to hypertensive hemorrhage such as the pons, thalamus, or basal ganglia. The enhancing portion of glioblastoma corresponds to an area of aberrant vascular proliferative change[24]; and therefore, perhaps is particularly susceptible to hemorrhage. Interestingly, patients with absence of enhancing tumor did not develop ICH. However, the presence or size of enhancing tumor need not be a contraindication to initiating anticoagulation as there was no difference between median diameter of enhancing portion of tumor in patients with ICH and those without ICH. This latter finding is consistent with the absence of a relationship between extent of surgical resection on initial diagnosis and ICH incidence. However, gross total resection with elimination of all enhancing tumor might decrease the incidence of ICH before enhancing tumor recurrence.

Our results support the general consensus within the neuro-oncology field that anticoagulation for VTE has an acceptable risk-benefit ratio in appropriately selected glioblastoma patients. The method of anticoagulation did not affect the patient's risk of developing ICH. Use of VEGF inhibitors in conjunction with anticoagulation was not associated with an increased incidence of ICH. Finally, we demonstrate that although the enhancing component of the tumor appears susceptible to hemorrhage, the diameter of the enhancing part is not predictive of developing ICH.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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